Introduction to rat genomics and rat populations

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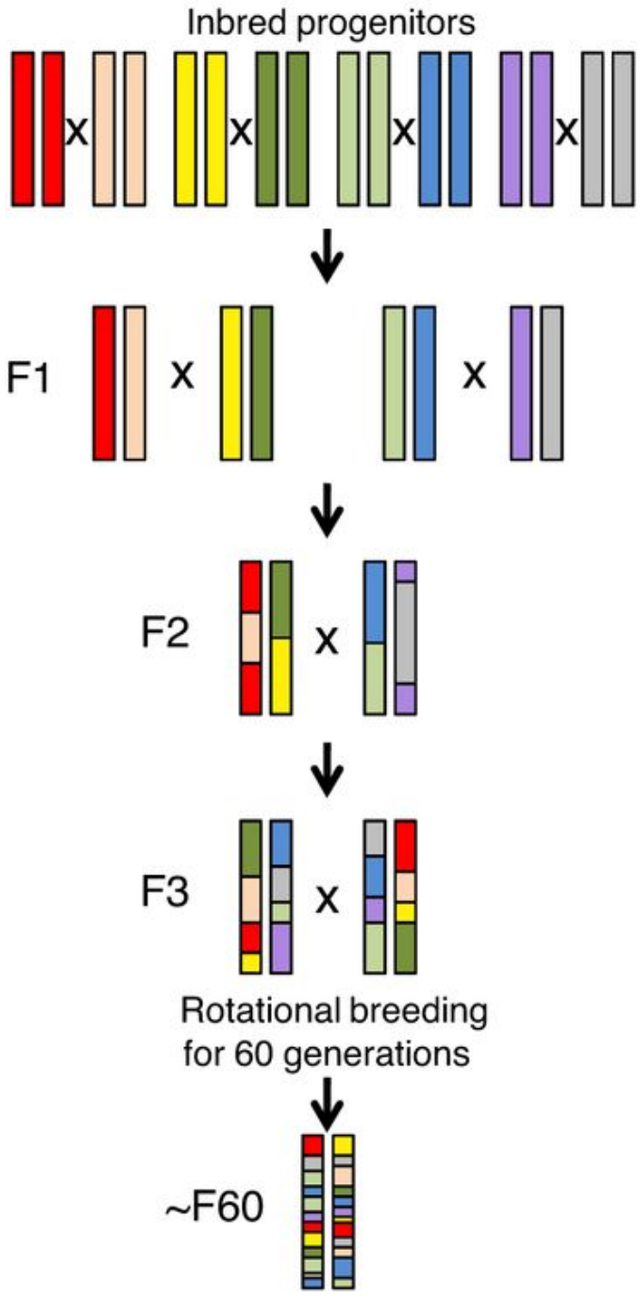
Outline

- Heterogenous Stock
- Inbred Strains
- Recombinant Inbred Strains
- Hybrid Rat Diversity Panel
- Reduced Complexity Cross
- Selected Lines

Heterogeneous Stock Rats

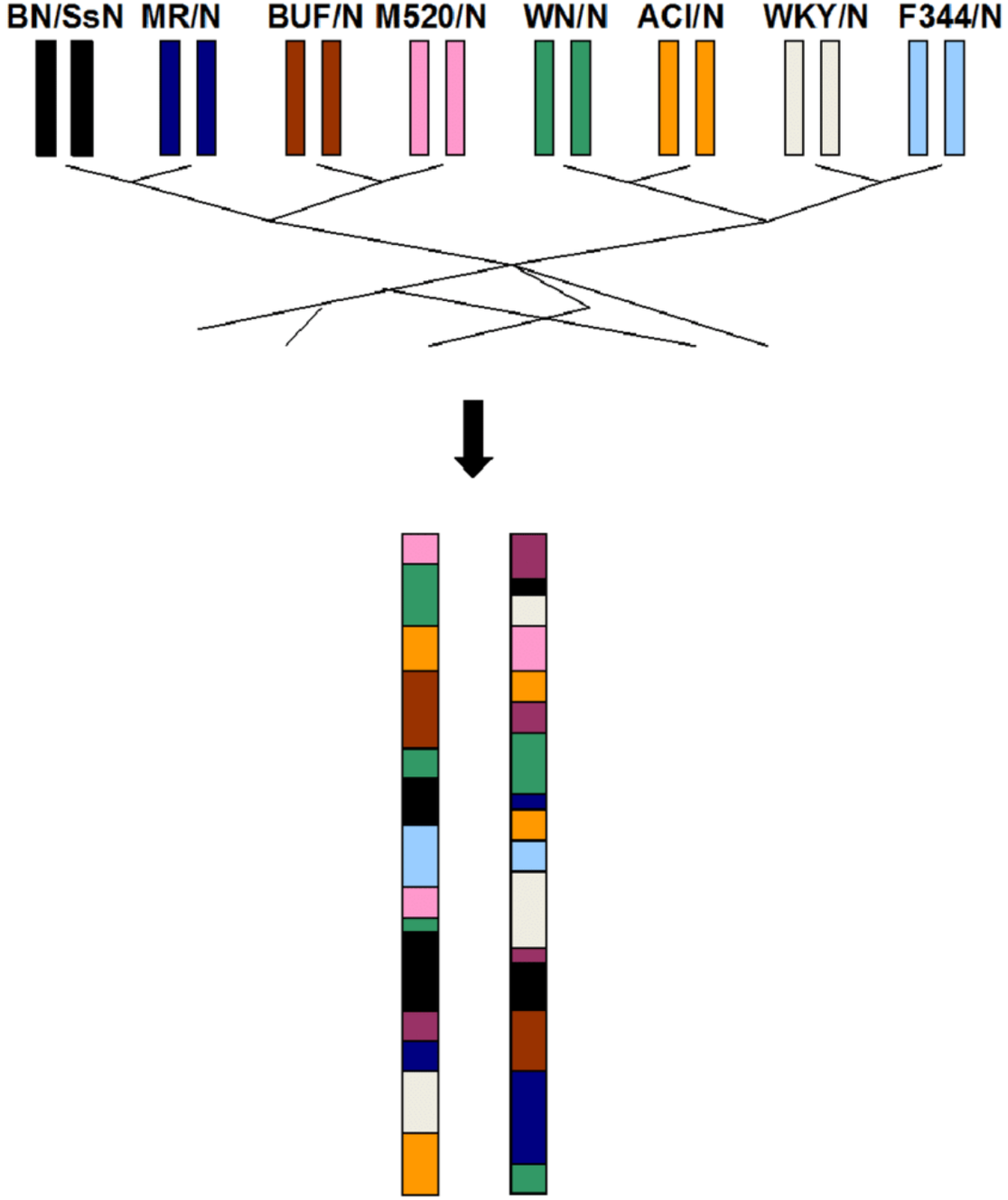
Heterogeneous Stock Rodent Populations



- Started 8 genetically diverse inbred strains
- Rotational breeding to minimize inbreeding
- Rats are genetic mosaics of the 8 progenitor strains
- Each rat is genetically distinct
- Currently used in at least 8 different NIH grants including the NIDA Center for Genetics Studies of Drug Abuse in Outbred Rats (A. Palmer, UCSD)

Yau AC, Holmdahl R. Dis Model Mech. 2016 Oct 1;9(10):1111-1123.

N/NIH Heterogeneous Stock Rats



- First established in 1984 at NIH
- Currently being breed at Wake Forest University under the supervision of Dr. Leah Solberg Woods
- Average distance between recombination events in the centiMorgan range allowing genetic mapping to only a few Mb

Advantages of HS Rats

- Average distance between recombination events in the centiMorgan range allowing genetic mapping to only a few Mb

- Minor allele frequencies are not likely to drop below 12.5% (i.e., 1/8)

- Homozygous and heterozygous individual observed at population SNPs

- Complete genomes are available for the 8 progenitor strains (Baud et al 2014) therefore potential causal SNPs can be identified through ‘merge’ analyses (Solberg Woods et al 2017)

Examples of Current HS Resources

- Leah Solberg Woods (WFU) - breeding facility
- Abraham Palmer (UCSD) and the NIDA Center for Genetics Studies of Drug Abuse in Outbred Rats - genotyping, phenotyping, and data integration
- Rob Williams (UTHSC), Saunak Sen (UTHSC), and colleagues - development of mapping methods and software
- Olivier George (UCSD) - Cocaine and Oxycodone Biobanks (https://www.cocainebiobank.org/ and https://www.oxycodonebiobank.org/)

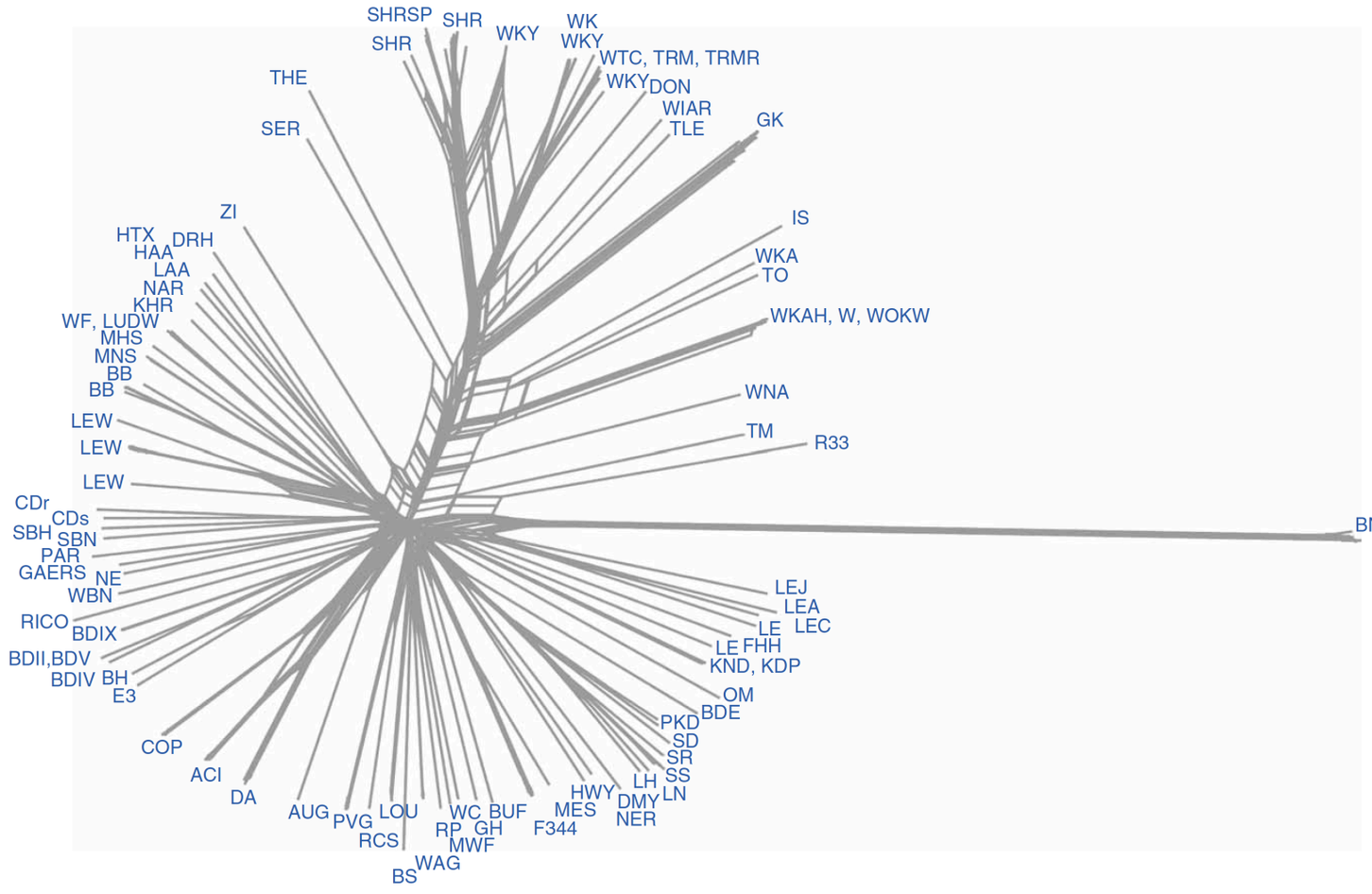
Inbred Rats

Introduction to Inbred Rats

- Generated from brother-sister mating (over 20 consecutive generations)

- After 20 generations, 98.7% of alleles are homozygous; after 40 generations, 99.98% of alleles are homozygous (Silvers 1995)

- Animals within a strain are analogous to monozygotic twins



STAR Consortium, et al. SNP and haplotype mapping for genetic analysis in the rat. Nat Genet. 2008 May;40(5):560-6.

Advantages of Inbred Rats

- Genetic identity is retained over generations
- Accumulative genetic and phenotype data across labs
- Ideal genetic controls for studying interventions/ environmental effects
- Biological replicates allow for the estimation and isolation of environmental variance

Examples of Current Inbred Resources

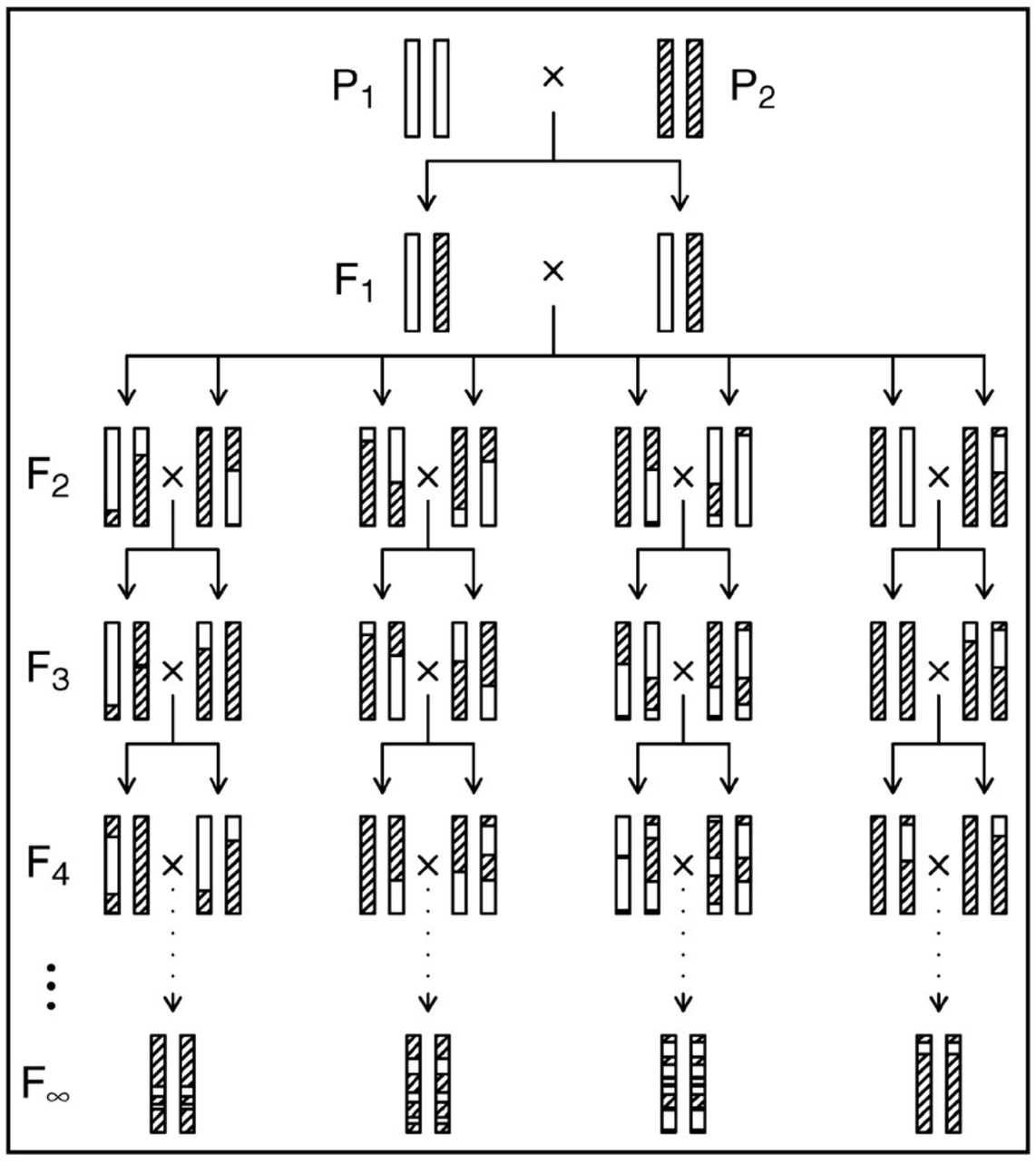
- Mary Shimoyama and Rat Genome Database (MCW) - detailed descriptions/annotation and DNA sequence information (more to come!)

- Elizabeth Bryda and the Rat Resource and Research Center (RRRC; Univ of Missouri) - embryo and live strain repository and repository for rat embryonic stem cells

- Charles River/Envigo - companies that sell inbred strains

Recombinant Inbred Rats

Introduction to Recombinant Inbred Strains/Panel



- Generated from two genetically diverse inbred rat strains
- F1/F2 are generated from intercrossing
- After F2, brother-sister mating to develop inbred strains

Advantages of Recombinant Inbred Panels

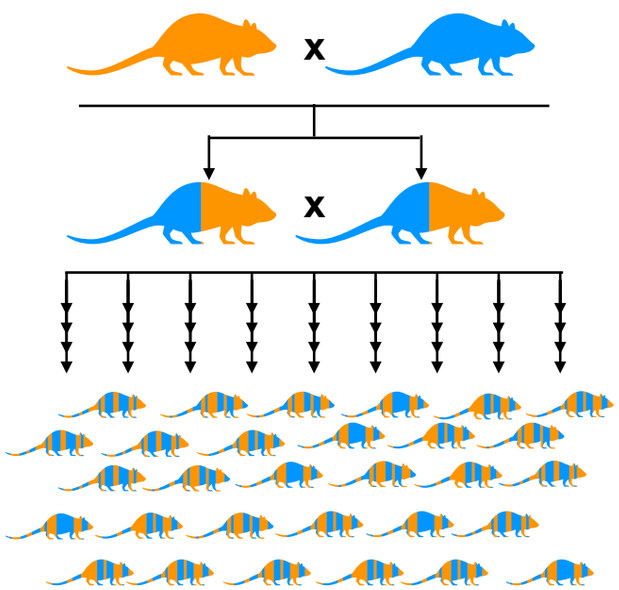
- Each strain is a mosaic of the two progenitor strains

- Most variants have a minor allele frequency close to 50% (i.e., high power)

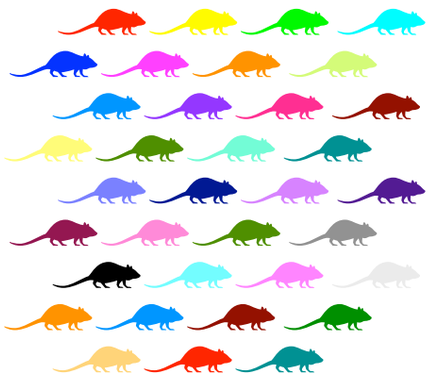
- Within strain, animals are similar to monozygotic twins; across strains, animals are similar to dizygotic twins

Hybrid Rat Diversity Panel

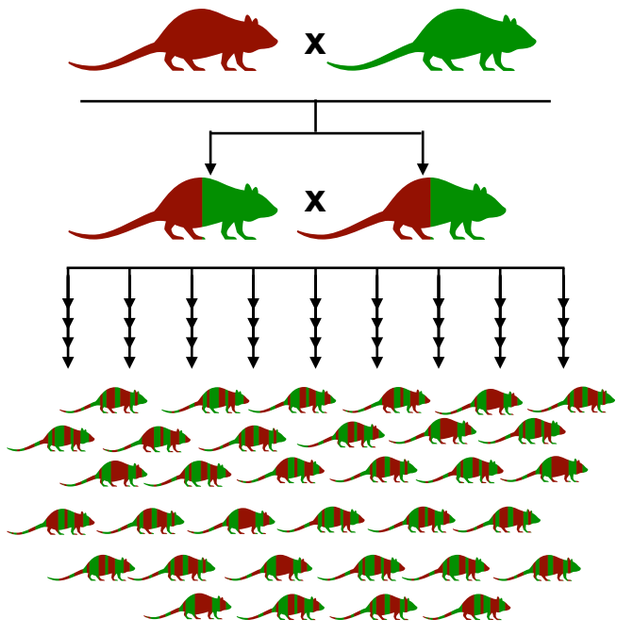
Introduction to Hybrid Rat Diversity Panel



HXB/BXH Recombinant Inbred Panel (30 strains)



Divergent Classic Inbred Strains (35 strains)



FXLE/LEXF Recombinant Inbred Panel (34 strains)

Advantages of HRDP

- ***Power*** gained from RI panel and ***precision*** gained from classic inbred panel
    - power to detect loci that contribute 10-20% to genetic variance
    - high resolution mapping (median haplotype block size = 225 kb)
- Power to detect GXE effects through static genetic composition

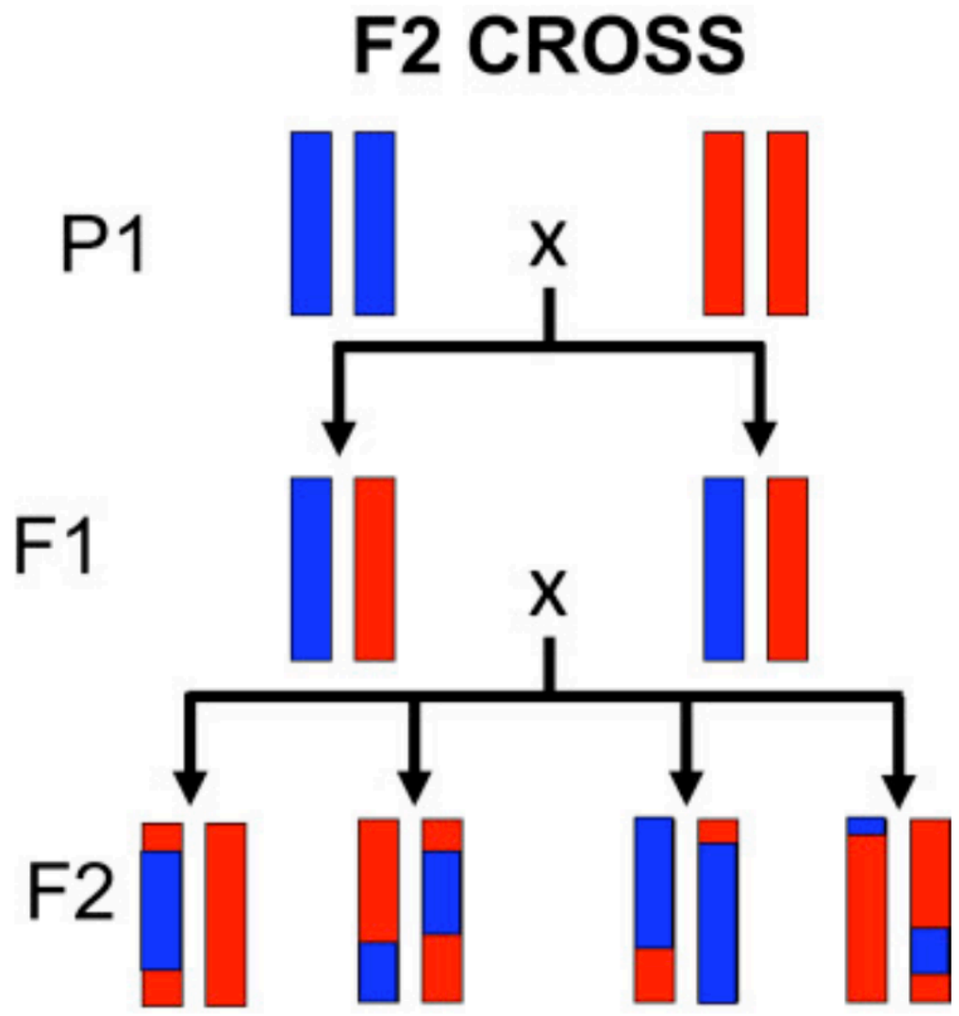
Examples of Current HRDP Resources

- Melinda Dwinell and colleagues (MCW) - rederivation/ breed of strains

- Boris Tabakoff, Paula Hoffman, and Laura Saba (UCAMC) - transcriptome information from brain, liver, heart, and kidney

Reduced Complexity Cross

Introduction to Reduced Complexity Cross



- Similar to recombinant inbred panel with the exception that the two progenitor strains are genetically similar (i.e., substrains of the same strain) but differ on a key phenotype

- Like an F2 cross, breeding stops at F2 generation for mapping traits

Bryant, Camron D., et al. “Chapter 8 - Reduced Complexity Cross Design for Behavioral Genetics.” In Molecular-Genetic and Statistical Techniques for Behavioral and Neural Research, edited by Robert T. Gerlai, 165–90. San Diego: Academic Press, 2018.

Advantages of RCC

- Although similarly sized, QTL regions in an RCC include fewer candidate genetic variants

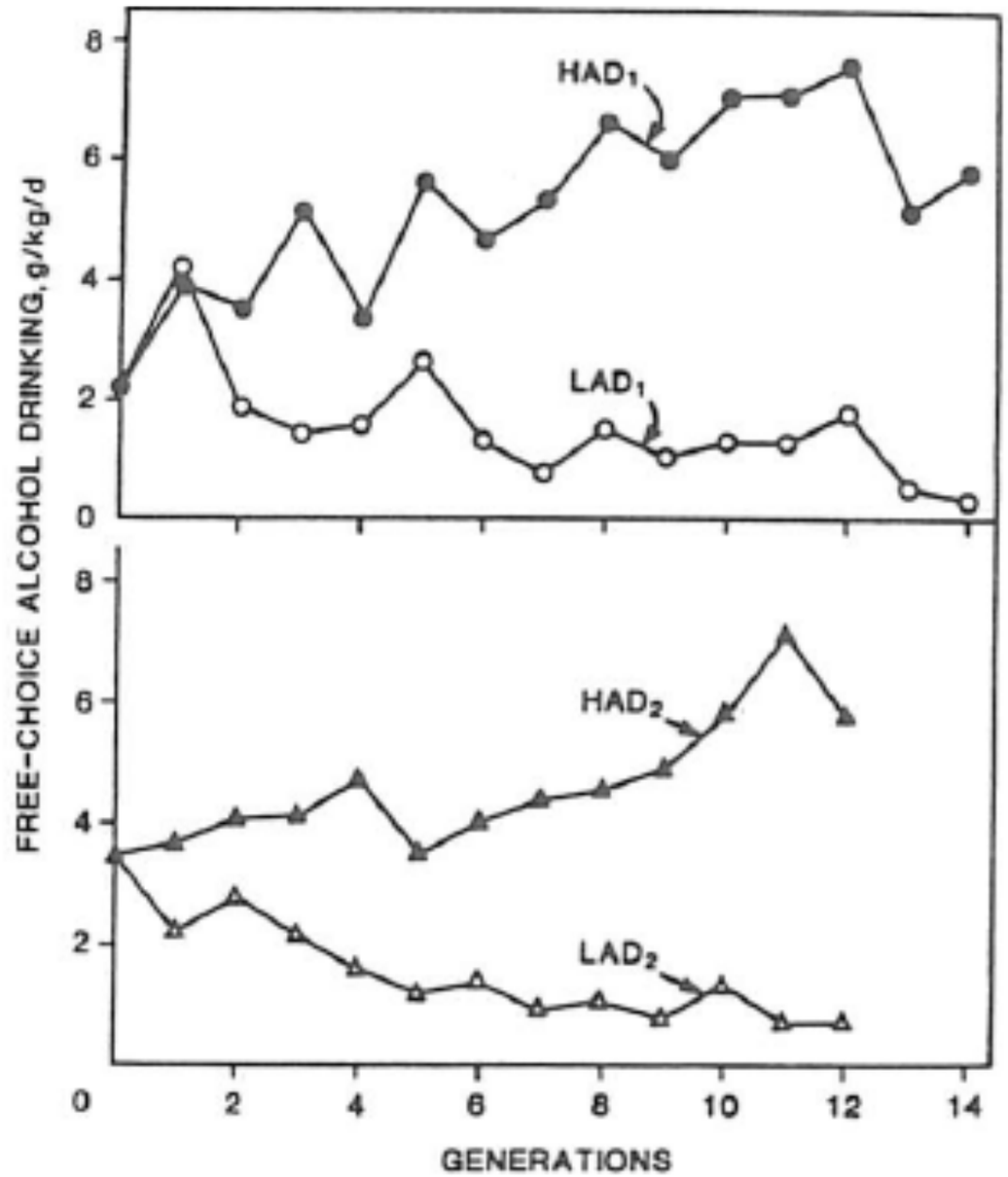
- Rapid turn around from mapping to causal gene/variant (e.g., approximately 3 years)

Selected Lines

Introduction to Selected Lines

- Lines of rats that are bred through selection with the intent to “fix” regions of the genome associated with selection trait, while remainder of genome varies randomly

- Similar to a case/control study:
  - Represents the extremes of the complex trait used for selection



Li T-K, Lumeng L, and Doolittle DP (1993). Selective breeding for alcohol preference and associated responses. Behavior Genetics 23(2):163-170

Advantages of Selected Lines

- Proof of genetic etiology of trait
- Extreme trait values can be generated
- Observe co-segregating traits
- Molecular traits can be observed in animals that have not been exposed to the behavioral paradigm or pharmacologic/toxic challenge

Examples of Current Selected Line Resources

- Indiana University School of Medicine - P/NP, HAD/LAD rats for alcohol consumption

- Richard Radcliffe (UC-AMC) - IHAS/ILAS, IAT/INT for alcohol sensitivity and tolerance, respectively